DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 14 1998

NDA 19-614/S-024

Lederle Laboratories
Attention: Ms. Diane Mitrione
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Mitrione:

Please refer to your April 29, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Verelan (verapamil HCI) Capsules.

We acknowledge receipt of your submission dated March 12, 1998.

This supplemental application provides final printed labeling revised as follows:

The entire **OVERDOSAGE** section was replaced with the following text:

> There is no specific antidote for verapamil overdosage; treatment should be supportive. Delayed pharmacodynamic consequences may occur with sustained-release formulations, and patients should be observed for at least 48 hours, preferably under continuous hospital care. Reported effects include hypotension, bradycardia, cardiac conduction defects, arrhythmias, hyperglycemia, and decreased mental status. In addition, there have been literature reports of noncardiogenic pulmonary edema in patients taking large overdoses of verapamil (up to approximately 9 g).
>
> In acute overdosage, gastrointestinal decontamination with cathartics and whole bowel irrigation should be considered. Calcium, inotropes (i.e., isoproterenol, dopamine, and glucagon), atropine, vasopressors (i.e., norepinephrine, and epinephrine), and cardiac pacing have been used with variable results to reverse hypotension and myocardial depression. In a few reported cases, overdose with calcium channel blockers that was initially refractory to atropine became more responsive to this treatment when the patients received large doses (close to 1 gram/hour for more than 24 hours) of calcium chloride. Calcium chloride is preferred to calcium gluconate since it provides 3 times more calcium per volume.Asystole should be handled by the usual measures including cardiopulmonary resuscitation. Verapamil cannot be removed by hemodialysis.

The following sentence was added to the PRECAUTIONS: **Drug Interactions** section:

> Aspirin: In a few reported cases, coadministration of verapamil with aspirin has led to increased bleeding times greater than observed with aspirin alone.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included in your March 12, 1998 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

Raymond J. Lipicky, M.D.
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